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Real-time changes in pulse pressure during a 10-second end-expiratory occlusion test reliably detect preload responsiveness

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Abstract

Background The end-expiratory occlusion (EEO) test detects preload responsiveness through changes in cardiac index (ΔCI) during a 15-second respiratory hold at end-expiration. We investigated the diagnostic accuracy of EEO-induced changes in arterial pulse pressure (ΔPP), especially when the duration of EEO is reduced to 10″ and 5″, and whether adding an end-inspiratory occlusion (EIO) improves this diagnostic accuracy.

Methods In 143 mechanically ventilated patients with sinus rhythm, EEO and EIO were performed while recording ΔCI and ΔPP values. Either a fluid bolus-induced ΔCI ≥ 15% or a passive leg raising-induced ΔCI ≥ 10% defined preload responsiveness. The effects of the EEO and EIO tests on PP and CI were evaluated as the percentage difference between values averaged either over the last five seconds of the 15-sec respiratory holds ($\Delta PP_{EEO-15''}$ and $\Delta PP_{EIO-15''}$, $\Delta CI_{EEO-15''}$ and $\Delta CI_{EIO-15''}$), or between the 5th and the 10th seconds of the 15-sec respiratory holds ($\Delta PP_{EEO-10''}$ and $\Delta PP_{EIO-10''}$, $\Delta CI_{EEO-10''}$ and $\Delta CI_{EIO-10''}$), or during the five first seconds of respiratory holds ($\Delta PP_{EEO-5''}$ and $\Delta PP_{EIO-5''}$, $\Delta CI_{EEO-5''}$ and $\Delta CI_{EIO-5''}$) and baseline.

Results Sixty-one (43%) patients were preload responders. Both $\Delta CI_{EEO-15''}$ and $\Delta CI_{EEO-10''}$ were higher in responders than in non-responders (5.8 [4.5–7.3]% vs. 1.1 [0.1–3.4]% and 3.0 [2.4–4.3]% vs. 0.6 [0.1–1.6]%, respectively; $p < 0.001$), whereas $\Delta CI_{EEO-5''}$ did not differ between responders and non-responders. $\Delta PP_{EEO-5''}$, $\Delta PP_{EEO-10''}$ and $\Delta PP_{EEO-15''}$ were significantly higher in responders than in non-responders (5.2 [2.8–8.7]% vs. 1.2 [0.3–2.8]%, 7.7 [5.0–12.4]% vs. 1.8 [0.5–3.1]% and 8.1 [5.1–11.8]% vs. 1.5 [0.5–3.0]%, respectively; $p < 0.001$). For detecting preload responsiveness, compared to the area under the receiver operating characteristic (AUROC) of $\Delta CI_{EEO-15''}$ (0.935 [0.881–0.969]), the AUROC of $\Delta CI_{EEO-10''}$ was similar (0.910 [0.851–0.951], $p = 0.410$), but the AUROC of $\Delta CI_{EEO-5''}$ was smaller (0.541 [0.456–0.625], $p < 0.001$); the AUROC of $\Delta PP_{EEO-15''}$ (0.913 [0.857–0.952], $p = 0.346$), and $\Delta PP_{EEO-10''}$ (0.912 [0.860–0.947], $p = 0.336$) were similar, but the AUROC of $\Delta PP_{EEO-5''}$ (0.834 (0.763–0.891, $p = 0.005$) was significantly smaller. Evaluation of $\Delta CI_{EEO+EIO}$ and $\Delta PP_{EEO+EIO}$ did not enhance reliability of the test at each test duration.

Conclusion In ventilated patients with sinus rhythm, real-time changes in PP during a 10-second EEO reliably detect preload responsiveness.

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SHOUT
SHARE
IT

Trial registration No. IDRCB 2010A0095942. Registered 04 January 2010.

Keywords Fluid responsiveness, Cardiac output, Fluid challenge, Passive leg Raising, Haemodynamic monitoring

Introduction

In mechanically ventilated patients, the end-expiratory occlusion (EEO) test has been developed to detect preload responsiveness by using heart-lung interactions [1, 2]. It consists in interrupting mechanical ventilation at end-expiration for 12 [3] to 30 [4, 5] sec, which stops the cyclic impediment in venous return created by each insufflation in positive pressure. Cardiac preload increases transiently and, in the case of preload responsiveness of both ventricles, cardiac output significantly increases [6]. Conversely, a respiratory hold performed at end-inspiration (end-inspiratory occlusion, EIO) decreases cardiac output to a larger extent in the case of preload responsiveness than in the case of preload unresponsiveness [7, 8]. When both EEO and EIO tests are combined, the absolute change in cardiac output is larger than during EEO alone. This may allow one to detect preload responsiveness with techniques measuring cardiac output that are not precise enough for detection of cardiac output changes induced by EEO alone [7, 8], even though discrepant results have been reported [9].

The main drawback of the EEO and EIO tests is that the respiratory hold must be rather long, which prevents its use in patients who are awake enough to interrupt ventilator occlusion. Durations ranging from 12 to 30 s have been used in published studies [2]. There are two reasons for this long duration. The first is that the increase in right cardiac preload must be transmitted to the left side after the pulmonary transit time. The second reason is that monitoring devices average cardiac output over several seconds, which delays the occurrence of its changes. For instance, the pulse wave analysis technique used in the first article describing the EEO test [6] uses a moving average of 12 s.

In this regard, monitoring the effects of EEO and EIO through continuous arterial pressure might be interesting, especially pulse pressure (PP), the changes of which are proportional to changes in cardiac output [10, 11]. During respiratory holds, PP values may be stable enough to use a moving average of a few seconds only. First, this would allow the test to be performed without any specific device measuring cardiac output. Second, this may allow the reduction of the duration of respiratory holds, as there is no moving average for PP, and increase the applicability of the test to patients who cannot sustain a 15-sec respiratory occlusion. In the seminal study demonstrating the reliability of the EEO test, changes in PP reliably detected preload responsiveness when measuring its changes during the last 5 s of a 15-sec EEO [6]. Nevertheless, shorter durations of EEO assessed through changes in PP, and the potential advantage of adding a shortened EIO to EEO, have not been tested yet.

Thus, in the present study, we investigated (i) whether an EEO test shorter than 15 s and performed by assessing its effects on PP reliably detects preload responsiveness, and (ii) whether adding an EIO to EEO improves the detection of preload responsiveness when their effects are assessed through changes in PP.

Methods

Patients

This retrospective analysis was conducted in patients prospectively included in previous studies by our group in whom EEO and EIO had been performed [12–16]. If patients had been included in two studies, only the data of the study published first were retained. All studies had been approved by an Institutional Review Board. All patients or next of kin had been informed about the study and consented to participate.

Inclusion criteria common to all studies were: (i) age ≥ 18 y.o., (ii) mechanical ventilation in volume assist-control mode, (iii) monitoring already in place with a transpulmonary thermodilution device, and (iv) decision of the attending physicians to perform a passive leg raising (PLR) test [12–15] or to infuse a 500-mL fluid bolus [7, 8]. Exclusion criteria common to all studies were (i) spontaneous breathing activity preventing 15-second respiratory holds, (ii) atrial fibrillation, (iii) venous compression stockings and abdominal hypertension [17], (iv) intracranial hypertension, and (v) refusal of the patient or next of kin to participate in the study.

Haemodynamic measurements

In all studies, patients were equipped with a jugular central venous catheter and a thermistor-tipped arterial catheter in the femoral artery connected to a pressure sensor to perform transpulmonary thermodilution (PiCCOplus or PiCCO2 device, Pulsion Medical Systems, Getinge, Feldkirchen, Germany). Cardiac index (CI) was measured intermittently by injecting three consecutive 15-mL boluses of cold saline and averaging the obtained CI values [18]. CI was also measured continuously through pulse contour analysis (CI_{pulse}) after flushing the arterial line and checking for the absence of under- and overdamping of the arterial pressure curve [18, 19]. Both the PiCCOplus and PiCCO2 devices average CI_{pulse} values with a moving average of 12 s and refresh the CI_{pulse} value displayed on the screen every second. Variables measured by transpulmonary thermodilution devices were continuously recorded through PiCCO-Win

software v.4-x to 6-x (Pulsion Medical Systems, Getinge, Felkirchen, Germany).

Arterial pressure was recorded through the femoral arterial catheter. Central venous pressure was measured at the base of the C wave at end-expiration, and the average of three successive respiratory cycles was calculated. Arterial and central venous pressure, cardiac rhythm and airway pressure were continuously and digitally recorded via HEM 4.2 software (Notocord, Croissy-sur-Seine, France). Respiratory variables such as positive end-expiratory pressure (PEEP), plateau pressure (Pplat), respiratory rate and tidal volume (Vt) were collected.

Respiratory settings

In all studies, patients were ventilated in the volume assist-control mode (Evita 4 or Infinity V500 (Dräger, Lübeck, Germany) or CARESCAPE R860 (General Electric Healthcare, Chicago, IL, USA)), with a tidal volume of 6 mL/kg of predicted body weight. The fraction of inspired oxygen (FiO_2) and respiratory rate were decided by the attending physician. Neuromuscular-blocking agents were used if clinically required. These settings were kept unchanged during the study period.

EEO and EIO

Before EEO and EIO, pulse contour analysis was calibrated via transpulmonary thermodilution and haemodynamic stability was ensured. The 15-second EEO or EIO manoeuvres were performed in a random order. Between both respiratory holds, CI_{pulse} and PP were allowed to return to baseline. After haemodynamic status had stabilised, a 15-second EIO test was performed (Fig. 1). After haemodynamic variables had stabilised again, a PLR test was performed [12–15] as previously reported [20] or a 500-mL fluid bolus was infused [7, 8]. No change in sedative drugs or catecholamines was allowed during the study time.

Data analysis

Effects of EEO and EIO on pulse pressure and cardiac index

The effects of the EEO and EIO tests on PP and CI were evaluated as the percentage difference between, on the one side, values averaged either over the last five seconds of the 15-sec respiratory holds ($\Delta PP_{EEO-15"}$ and $\Delta PP_{EIO-15"}$, respectively for PP and $\Delta CI_{EEO-15"}$ and $\Delta CI_{EIO-15"}$, respectively for CI), or between the 5th and the 10th seconds of the 15-sec respiratory holds ($\Delta PP_{EEO-10"}$ and $\Delta PP_{EIO-10"}$, respectively for PP and $\Delta CI_{EEO-10"}$ and $\Delta CI_{EIO-10"}$, respectively for CI) or during

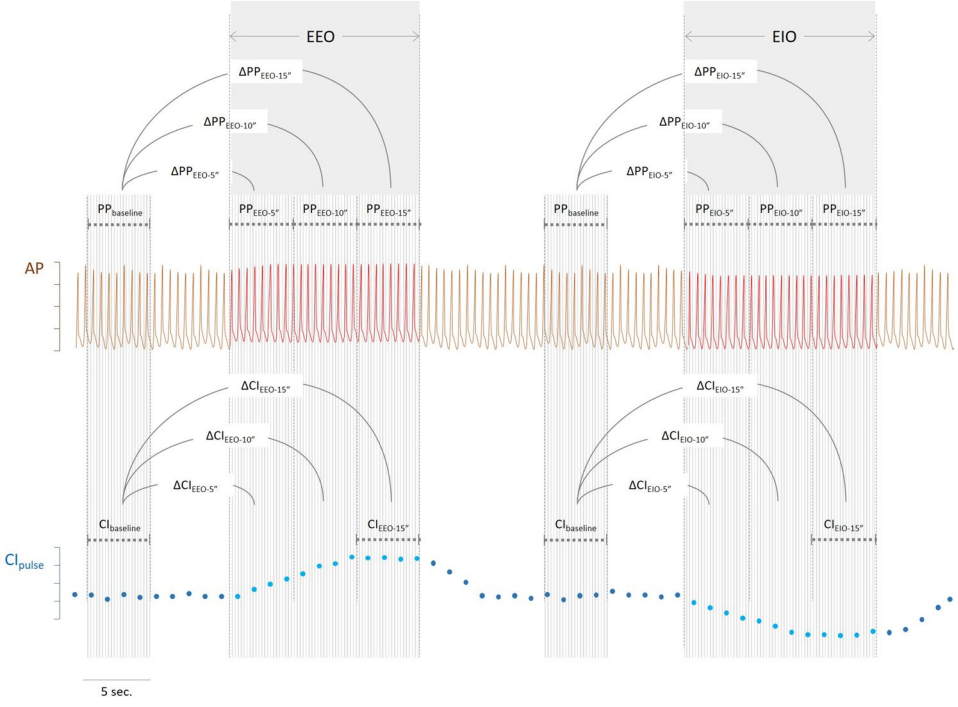

Fig. 1 Description of the calculation of changes in arterial pulse pressure (ΔPP) and of pulse contour-derived cardiac index (CI_{pulse}) during end-expiratory (EEO) and end-inspiratory (EIO) occlusions using theoretical arterial pressure traces and cardiac index $\Delta PP_{EEO-5"}$: changes in pulse pressure during the first 5 s of the end-expiratory occlusion, $\Delta PP_{EEO-10"}$: changes in pulse pressure between the 5 th and 10 th seconds of the end-expiratory occlusion, $\Delta PP_{EEO-15"}$: changes in pulse pressure during the last 5 s of the end-expiratory occlusion, $\Delta PP_{EIO-5"}$: changes in pulse pressure during the first 5 s of the end-inspiratory occlusion, $\Delta PP_{EIO-10"}$: changes in pulse pressure between the 5 th and 10 th seconds of the end-inspiratory occlusion, $\Delta PP_{EIO-15"}$: changes in pulse pressure during the last 5 s of the end-inspiratory occlusion, $\Delta CI_{EEO-15"}$: changes in cardiac index during the last 5 s of the end-expiratory occlusion, $\Delta CI_{EIO-15"}$: changes in cardiac index during the last 5 s of the end-inspiratory occlusion

the five first seconds of respiratory holds ($\Delta PP_{EEO-5''}$ and $\Delta PP_{EIO-5''}$, respectively for PP and $\Delta CI_{EEO-5''}$ and $\Delta CI_{EIO-5''}$, respectively for CI) and, on the other side, values averaged over five seconds at baseline (Fig. 1). The effects of combined EEO and EIO tests ($\Delta PP_{EEO+EIO-5''}$, $\Delta PP_{EEO+EIO-10''}$ and $\Delta PP_{EEO+EIO-15''}$ for PP and $\Delta CI_{EEO+EIO-5''}$, $\Delta CI_{EEO+EIO-10''}$ and $\Delta CI_{EEO+EIO-15''}$ for CI) were calculated as the sum of the relative changes in PP and CI observed during the corresponding EEO and EIO.

Definition of preload responsiveness

Preload responsiveness was defined as a PLR-induced increase in CI_{pulse} ≥10% [12–15] or a fluid-induced increase in CI_{pulse} ≥15% [7, 8] when fluid challenge had been performed.

Statistical analysis

Data are expressed as mean ± SD or median [IQR], depending on data distribution. The normality of data distribution was evaluated visually. Pairwise comparisons of data were done with the paired Student's *t* test or Wilcoxon test, depending on data distribution. The two-tailed Student *t* test or Mann-Whitney-U test, depending on data distribution, was used to compare preload responders and preload non-responders. The area under the receiver operating characteristic curve (AUROC) was calculated for the ability of changes in PP and CI during the various respiratory holds to detect preload responsiveness. The best diagnostic threshold was determined as the one providing the best Youden index. AUROCs were compared using the Hanley-McNeil test for repeated comparisons, and a Bonferroni correction was used for multiple comparisons. Also, we calculated the least significant change (LSC) of PP in 10 patients chosen at random in our population, as previously explained [21]. Briefly, the coefficient of error – the ratio of the coefficient of variation over √(number of replicates) – was multiplied by 1.96 and √2, in order to identify the minimum change measured that can be trusted as a real change of measurement.

Statistical significance was set at a p value < 0.05. Statistical analysis was performed with MedCalc software 19.6 (Mariakerke, Belgium).

Results

Patients

We retrieved data from 143 patients enrolled between May 2016 and December 2019, including 61 preload responders and 82 preload non-responders. Twenty-one patients (12%) were excluded from the analysis for inability of sustaining a respiratory hold. Preload responsiveness was defined most frequently according to PLR test results (121 patients). Seventy-nine patients (55%) had acute respiratory distress syndrome (ARDS) and no patient was in prone position during the study period. Forty-two patients had a past medical history of chronic obstructive pulmonary disease and ten patients of asthma. Patients were enrolled after 1.0 [1.0–3.0] days from shock onset, with no difference between responders and non-responders (1.0 [1.0–3.0] days vs. 1.0 [1.0–3.0] days, respectively, $p > 0.05$). The remaining patient characteristics are shown in Table 1.

Changes in cardiac index induced by the respiratory occlusions

The changes in haemodynamic variables are shown in Table 2. $\Delta CI_{EEO-5''}$ did not differ between responders and non-responders (0.7 [0.4–1.4]% vs. 0.3 [0.1–1.7]%, respectively, $p = 0.22$). $\Delta CI_{EEO-10''}$ was significantly higher in responders than in non-responders, (3.0 [2.4–4.3]% vs. 0.6 [0.1–1.6]%, respectively, $p < 0.001$). This was also the case for $\Delta CI_{EEO-15''}$ (5.8 [4.5–7.3]% vs. 1.1 [0.1–3.4]%, respectively, $p < 0.001$).

$\Delta CI_{EIO-5''}$ was significantly higher in responders than in non-responders (−1.4 [−2.8 – −0.7]% vs. −0.0 [−0.3 – −3.3]%, respectively, $p = 0.02$). This was also the case for $\Delta CI_{EIO-10''}$ (−4.8 [−7.3 – −2.8]% vs. −0.6 [−1.3–0.0]%, respectively, $p = 0.002$) and for $\Delta CI_{EIO-15''}$ (−7.9 [−11.2 – −6.5]% vs. −3.5 [−4.3 – −1.4]%, respectively, $p < 0.001$).

$\Delta CI_{EEO+EIO-5''}$ was significantly higher in responders than in non-responders (1.9 [1.0–6.3]% vs. 0.4 [0.1–1.6]%, respectively, $p = 0.03$). This was also the case for $\Delta CI_{EEO+EIO-10''}$ (8.9 [5.4–12.4]% vs. 1.5 [0.9–2.3]%, respectively, $p < 0.001$) and $\Delta CI_{EEO+EIO-15''}$ (15.0 [12.7–18.5]% vs. 4.5 [2.8–7.1]%, respectively, $p < 0.001$).

Changes in pulse pressure induced by the respiratory occlusions

The LSC of PP among the 10 randomly chosen patients was 2.0%. $\Delta PP_{EEO-5''}$ was significantly higher in responders than in non-responders (5.2 [2.8–8.7]% vs. 1.2 [0.3–2.8]%, respectively, $p < 0.001$). This was also the case for $\Delta PP_{EEO-10''}$ (7.7 [5.0–12.4]% vs. 1.8 [0.5–3.1]%, respectively, $p < 0.001$ – Supplementary material S1) and for $\Delta PP_{EEO-15''}$ (8.1 [5.1–11.8]% vs. 1.5 [0.5–3.0]%, respectively, $p < 0.001$) (Fig. 2).

$\Delta PP_{EIO-5''}$ was significantly higher in responders than in non-responders (−6.0 [−8.8 – −3.2]% vs. −2.6 [−5.4 – −0.5]%, respectively, $p = 0.031$). This was also the case for $\Delta PP_{EIO-10''}$ (−9.5 [−12.7 – −5.7]% vs. −4.7 [−7.0 – −1.4]%, respectively, $p < 0.001$) and for $\Delta PP_{EIO-15''}$ (−9.4 [−12.8 – −6.2]% vs. −4.8 [−7.1 – −1.7]%, respectively, $p < 0.001$) (Fig. 2).

$\Delta PP_{EEO+EIO-5''}$ was significantly higher in responders than in non-responders (11.3 [8.2–15.4]% vs. 3.9 [1.2–7.7]%, respectively, $p < 0.001$). This was also the case for $\Delta PP_{EEO+EIO-10''}$ (17.2 [12.9–24.3]% vs. 6.8 [2.1–10.7]%,

Table 1 Patient characteristics

Age (years)	
Responders (n = 61)	62 [56–76]
Non-responders (n = 82)	63 [53–68]
Male gender (n, %)	
Responders (n = 61)	49 (80%)
Non-responders (n = 82)	67 (83%)
Body mass index (kg/m^2)	
Responders (n = 61)	26.0 [23.6–26.6]
Non-responders (n = 82)	26.6 [20.9–28.8]
SAPS II on inclusion	
Responders (n = 61)	55 [44–62]
Non-responders (n = 82)	51 [48 –59]
Type of shock (n, %)	
Septic	
Responders (n = 61)	58 (95.1%)
Non-responders (n = 82)	74 (90.2%)
Cardiogenic	
Responders (n = 61)	0 (0%)
Non-responders (n = 82)	3 (3.7%)
Hypovolemic	
Responders (n = 61)	3 (4.9%)
Non-responders (n = 82)	2 (2.5%)
Distributive non-septic	
Responders (n = 61)	0 (0%)
Non-responders (n = 82)	3 (3.7%)
Time from shock onset to inclusion (days)	
Responders (n = 61)	2.0 [1.0–3.0]
Non-responders (n = 82)	1.0 [1.0–3.0]
Acute respiratory distress syndrome (n, %)	
Responders (n = 61)	35 (57.4%)
Non-responders (n = 82)	44 (53.7%)
Lactate (mmol/L)	
Responders (n = 61)	2.9 [2.2–3.8]
Non-responders (n = 82)	2.5 [2.0–2.9]
Patients under norepinephrine (n, %)	
Responders (n = 61)	55 (90.2%)
Non-responders (n = 82)	77 (95.6%)
Dose of base norepinephrine (µg/kg/min)	
Responders (n = 61)	0.33 [0.11–0.67]
Non-responders (n = 82)	0.38 [0.31–0.80]
Ventilator settings	
Tidal volume (mL/kg of PBW)	
Responders (n = 61)	5.8 [5.1–6.1]
Non-responders (n = 82)	5.7 [5.0–6.0]
Respiratory rate (breaths/min)	
Responders (n = 61)	24 [20–27]
Non-responders (n = 82)	28 [25–32]
Fraction of inspired oxygen	
Responders (n = 61)	0.43 [0.40–0.65]
Non-responders (n = 82)	0.50 [0.50–0.60]
Total PEEP (cmH$_2$O)	
Responders (n = 61)	10 [8–14]
Non-responders (n = 82)	12 [10–15]
Plateau pressure (cmH$_2$O)	
Responders (n = 61)	24 [20–29]
Non-responders (n = 82)	26 [24–29]
Patients with intrinsic PEEP (n, %)	
Responders (n = 61)	22 (36.0%)
Non-responders (n = 82)	28 (34.1%)
Intrinsic PEEP (cmH$_2$O)	
Responders (n = 22)	3 [1–7]
Non-responders (n = 28)	3 [1–8]
Patients receiving neuromuscular blockers (n,%)	
Responders (n = 61)	23 (37.7%)
Non-responders (n = 82)	20 (24.7%)
Mortality at 28 days (n, %)	
Responders (n = 61)	18 (29.5%)
Non-responders (n = 82)	23 (28.4%)

PEEP positive end-expiratory pressure, *PBW* predicted body weight, *SAPS II* Simplified Acute Physiologic Score II.

respectively, $p < 0.001$) and $\Delta PP_{EEO+EIO-15''}$ (17.7 [12.3–24.1]% vs. 6.3 [12.7–9.8]%, respectively, $p < 0.001$).

Detection of preload responsiveness

With a cut-off value of 2.1%, the AUROC of $\Delta CI_{EEO-10''}$ was not significantly different from the one of $\Delta CI_{EEO-15''}$ in the ability of detecting preload responsiveness (0.910 [0.851–0.951] vs. 0.935 [0.881–0.969], respectively; $p = 0.801$). On the contrary, $\Delta CI_{EEO-5''}$ could not detect preload responsiveness (Supplementary material S2). Also, there was no difference between the AUROC of $\Delta CI_{EEO-15''}$ and that of $\Delta PP_{EEO-15''}$.

As for PP, the AUROC of $\Delta PP_{EEO-10''}$ was 0.912 [0.860–0.947], with sensitivity of 86.9 [75.8–94.2]%, specificity of 80.5 [70.3–88.4]% and a cut-off value of 3.7%. It did not differ from the AUROC of $\Delta PP_{EEO-15''}$ (0.913 [0.857–0.952], $p = 0.983$) but was significantly higher than the one of $\Delta PP_{EEO-5''}$ (0.834 [0.763–0.891], $p = 0.001$) (Fig. 3).

When EEO and EIO were combined, analogous results were observed, with no differences between the AUROCs of $\Delta PP_{EEO+EIO-15''}$ and $\Delta PP_{EEO+EIO-10''}$ (0.899 [0.837–0.943] and 0.882 (0.818–0.930), respectively) but with the one of $\Delta PP_{EEO+EIO-5''}$ (0.832 [0.761–0.889]) that was significantly lower.

When patients were stratified according to the PEEP level, similar results were observed among patients in the lowest and in the highest quartile of PEEP level (Supplementary material S3).

Discussion

This study demonstrates that, in mechanically ventilated patients with sinus rhythm, real-time changes in PP during a 10-second EEO reliably detect preload responsiveness.

The EEO test is one of the methods that use heart-lung interactions to test preload responsiveness in mechanically ventilated patients [22]. Specifically, it uses the transient increase in cardiac preload created by stopping

Table 2 Haemodynamic variables during end-expiratory (EEO) and end-inspiratory (EIO) occlusions depending on the timing of measurements in preload responders and non-responders

	During the 5 first seconds of EEO	Between the 5 th and the 10 th seconds of EEO	Between the 10 th and the 15 th seconds of EEO	During the 5 first seconds of EIO	Between the 5 th and the 10 th seconds of EIO	Between the 10 th and the 15 th seconds of EIO
Heart rate (beats/min)						
Preload responders	96 [84–108]	96 [84–120]	96 [84–108]	96 [72–108]	96 [84–108]	96 [84–108]
Preload non-responders	84 [72–99]	84 [72–108]	84 [74–108]	84 [72–96]	84 [72–108]	84 [72–107]
Systolic arterial pressure (mmHg)						
Preload responders	116 [106–130]	118 [108–132]	120 [109–132]	107 [98–125]	106 [95–122]	104 [94–124]
Preload non-responders	123 [110–143]*	123 [111–145]	123 [112–144]	120 [109–136]*	119 [108–134]*	120 [107–133]*
Diastolic arterial pressure (mmHg)						
Preload responders	56 [51–63]	59 [52–65]	59 [51–65]	58 [52–64]	56 [51–61]	55 [50–61]
Preload non-responders	62 [54–67]*	62 [54–68]	62 [54–67]	63 [55–68]*	60 [54–61]*	60 [54–67]*
Arterial pulse pressure (mmHg)						
Preload responders	62 [45–79]	63 [44–78]	65 [47–75]	55 [38–66]	54 [37–67]	53 [41–66]
Preload non-responders	65 [50–78]	64 [50–78]	65 [50–78]	60 [47–73]*	60 [46–73]*	61 [48–74]*
Cardiac index (L/min/m^2)						
Preload responders	2.1 [2.0 3.3]	2.2 [2.0–3.4]	2.2 [2.0–3.5]	2.2 [2.0–2.6]	2.1 [1.9–2.6]	2.0 [1.9–2.5]
Preload non-responders	3.5 [2.4–4.3]	3.5 [2.4–4.3]	3.6 [2.5–4.2]	3.6 [2.4–4.1]	3.5 [2.3–4.1]	3.3 [2.2–3.4]*

N = 61 preload responders and 82 preload non-responders

Results are expressed as median [interquartile range]

* $p < 0.05$ vs. preload responders

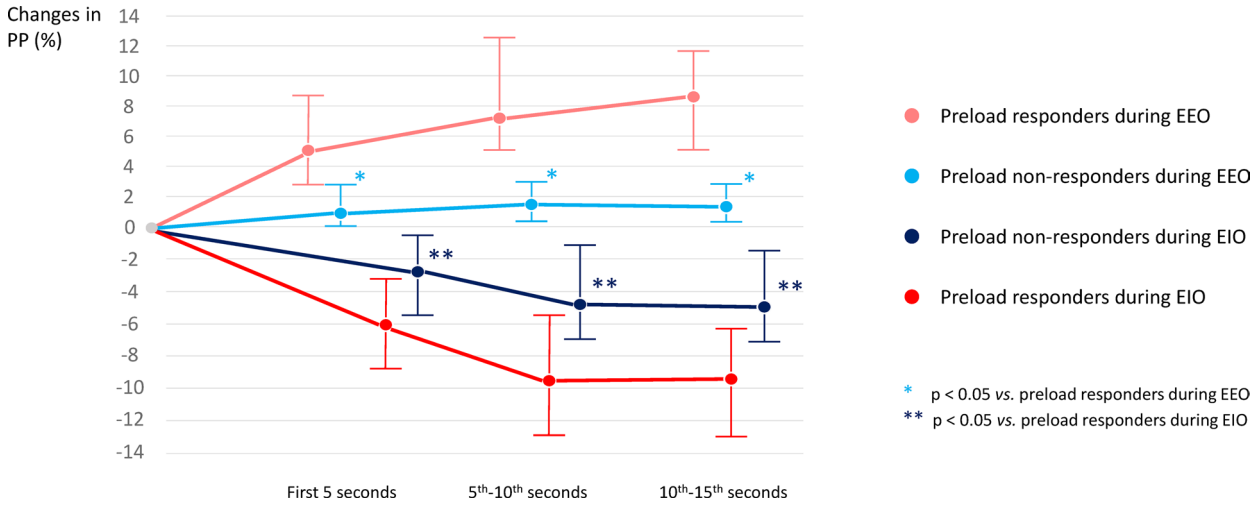

Fig. 2 Percentage changes in arterial pulse pressure (ΔPP) during end-expiratory (EEO) and end-inspiratory (EIO) occlusion in preload responders and preload non-responders depending on the time of measurements

positive pressure ventilation for a few seconds. The present study confirms previous ones showing that changes in CI_{pulse} during a 15-sec EEO detect preload responsiveness with high accuracy [2].

Our goal was to investigate ways to circumvent the two main limitations of the EEO test, i.e., its relatively long duration and the need for a device monitoring cardiac output [1]. In particular, we investigated the advantage of combining EIO and EEO, as we previously demonstrated that it reliably predicts fluid responsiveness when using ultrasound techniques [7, 8], which are less precise than pulse contour analysis [21]. We also investigated the ability of PP changes to reflect changes in cardiac output over a shorter period of time.

First, the present study confirms that a 15-second EEO detects preload responsiveness when PP, averaged over the last 5 s of the hold, is used to assess its effects. This had been shown in the first study describing the EEO test [6], but it has not been re-evaluated since then. Second, the EEO-induced changes in PP still reliably detect

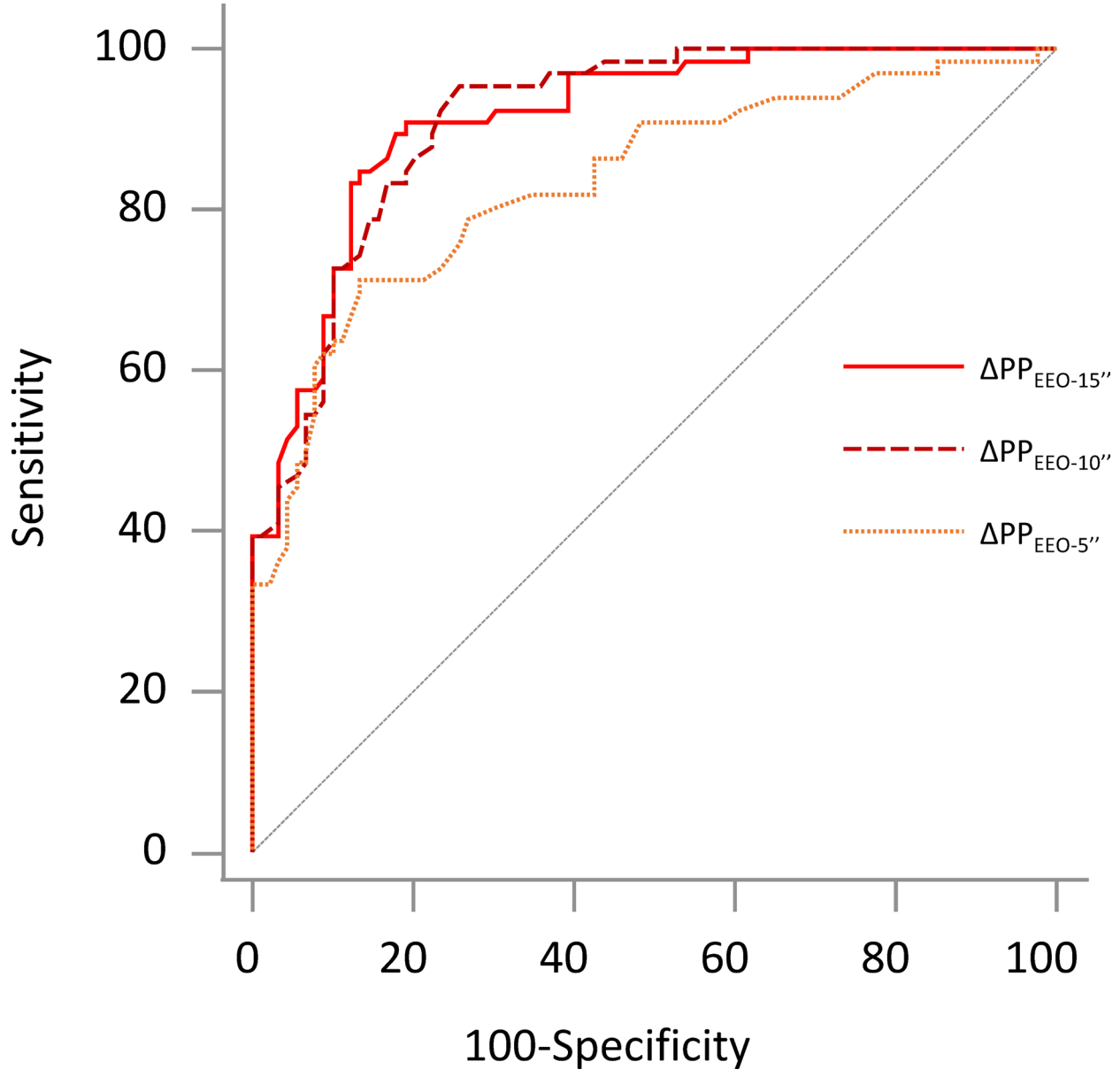

Fig. 3 Area under the receiver operating characteristic curves for changes in arterial pulse pressure (ΔPP) during end-expiratory occlusions (EEO) to detect preload responsiveness. $\Delta PP_{EEO\text{-}5''}$: changes in pulse pressure during the first 5 seconds of the end-expiratory occlusion, $\Delta PP_{EEO\text{-}10''}$: changes in pulse pressure between the 5th and 10th seconds of the end-expiratory occlusion, $\Delta PP_{EEO\text{-}15''}$: changes in pulse pressure during the last 5 seconds of the end-expiratory occlusion.

preload responsiveness when assessed between 5 and 10 s, with an AUROC larger than 0.90. This raises the possibility of shortening the duration of the EEO test. This would likely increase the number of patients in whom the test can be performed without any spontaneous respiratory effort.

Third, combining EEO and EIO did not allow reduction in the time over which PP changes were assessed. However, the thresholds for tests' positivity were larger than those of EEO alone. Then, a reason for choosing to perform EIO + EEO may be that the EEO alone has induced changes in PP or CI that are close to the diagnostic thresholds. The haemodynamic effects of EIO alone, on either CI or PP and whatever the length of measurement, were less reliable in detection of preload responsiveness than the effects of EEO.

For clinical practice, our study shows that, provided that an arterial line is present, no cardiac output monitor is necessary to assess the effects of EEO. However, the current bedside monitors do not display the PP value, which must be calculated from systolic and diastolic arterial pressure values. Moreover, our study shows that the

duration of EEO could be reduced to 10 s when its effects are assessed on PP rather than on CI. Nevertheless, we averaged PP values over 5 s, which again is not automatically performed by bedside monitors. Our results suggest that bedside monitors could be improved by directly displaying PP values. This would allow automatic and averaged measurements of PP changes during interventions such as EEO, and improve the precision for assessing PP changes. The bedside applicability of the method may be improved in this way. Regarding the effects of EEO on CI, it must be noted that the thresholds indicating tests' positivity were small, but higher than the least significant change reported for pulse contour analysis [23], which is a very precise technique. These results are not applicable to less precise monitoring techniques. Finally, it must be emphasized that our results are only applicable to patients without cardiac arrhythmia and any triggering inspiration during expiratory and inspiratory pauses.

The first limitation of this research is that the current analysis was retrospectively performed on the data of previous studies, albeit prospectively acquired. Second, in most studies, preload responsiveness was defined according to the effects of PLR, not of a fluid bolus. However, the evidence is nowadays strong that PLR detects preload responsiveness. Also, we could not retrieve the total amount of fluids administered to the patients before study inclusion. Third, we did not evaluate whether a sequence of shortened EIO + EEO with no interruption would improve the reliability of the combined tests. This manoeuvre may have induced larger changes in cardiac output and PP, and limited some false positives, especially in those patients for whom a titrated vascular filling is particularly important (severe ARDS patients, cardiogenic shock). Fourth, we did not calculate our sample size a priori, but rather included as many patients as allowed by the previous studies of our group. Finally, we assessed the absence of spontaneous breathing by observing the pressure curve of the ventilator. Some mild respiratory efforts may have been missed, while the monitoring of oesphageal pressure would have allowed us to detect them. However, their hemodynamic impact would likely be neglectable.

Conclusion

In ventilated patients with sinus rhythm, real-time changes in PP during a 10-second EEO detect preload responsiveness.

Abbreviations

AUROC	area under the receiver operating characteristics
CI	cardiac index
EEO	end-expiratory occlusion
EIO	end-inspiratory occlusion
PLR	passive leg raising
PEEP	positive end-expiratory pressure
PP	pulse pressure
Pplat	plateau pressure
Vt	tidal volume
ΔPP,	changes in pulse pressure
ΔCI	changes in cardiac index

Supplementary Information

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Supplementary Material 1

Author contributions

FG designed the study, acquired the data, performed data analysis and interpretation and wrote the manuscript.NDV acquired the data and contributed to data analysis.CL acquired the data.DA performed data analysis and interpretation. AP acquired the data.MJ acquired the data.RS acquired the data.IA acquired the data.AB acquired the data. J-LT designed the study, participated in data analysis and interpretation and contributed to writing the manuscript.XM designed the study, performed data analysis and interpretation and wrote the manuscript.All authors reviewed the manuscript and approved its final version.

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Data availability

Individual, de-identified participant data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Data collection of each study was approved by an independent ethics committee (Comité pour la Protection des Personnes, Ile-de-France VII). Informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript. The data were used anonymously.

Competing interests

FG has no conflicts of interest to disclose.NDV has no conflict of interest to discloseCL has received fees for lectures from Sedana MedicalDA has no conflict of interest to discloseAP has no conflict of interest to discloseMJ has no conflict of interest to discloseSR has no conflict of interest to discloseIA has no conflict of interest to discloseAB has no conflict of interest to discloseJLT has received fees for lectures from Masimo and Edwards Lifesciences. He has received fees for consulting from Pulsion Medical Systems (Getinge).XM has received fees for lectures from Baxter Healthcare, Philips, Masimo, AOP and Pulsion Medical Systems (Getinge). He has received fees for consulting from Pulsion Medical Systems (Getinge).

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